DENTAL DEFECTS AND RUBELLA EMBRYOPATHY: A CLINICAL STUDY OF FIFTY CHILDREN

by

Robert Jay Musselman

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INTRODUCTION

A woman who contracts rubella during pregnancy may deliver a child who manifests the combination of congenital defects of the eye, ear, heart and neurological system known as rubella embryopathy.

During the nation-wide epidemic of 1964, the state of Indiana recorded 13,037 cases of rubella, a six hundred per cent increase over the preceding year.[1] The resultant increase in children with rubella embryopathy has provided an opportunity to study the effect of the rubella virus on the fetus.

The effect of the rubella virus on the developing dentition has not been satisfactorily documented. The dental literature includes only five studies with contradictory findings. Two studies suggest that enamel hypoplasia and delayed eruption are common in children with rubella embryopathy. Three indicate that rubella has no effect on the teeth.

The present study was planned to investigate the incidence of dental defects in children with rubella embryopathy, and hopefully, to provide additional information regarding the effect of the rubella virus on the fetus.

REVIEW OF LITERATURE

Rubella is a mild communicable disease of childhood, occurring most commonly between the ages of six months and fourteen years, and characterized by a generalized rash and lymphadenopathy of the posterior cervical, retroauricular, and occipital nodes. When rash occurs, it often includes discrete red spots on the palate termed Forcheimer's spots. The rubella virus is spread by air-borne droplets and has an incubation period of approximately fourteen days. A single infection produces permanent immunity and an infant may carry its mother's immunity for six months after birth. Sever and his associates[2] indicate that rubella without rash occurs in 40 per cent of infected children.

The symptoms of rubella may be more severe in the infected adult and include such complications as arthritis and thrombocytopenia. While estimates of immunity to rubella range from 50 to 83 per cent of adult populations,[3,4] the observation has been made that 18.2 per cent of one group of infected females were fifteen years of age or more.[5]

The significance of this previously unexposed group of females of child-bearing age was first brought to light in 1941 by Gregg,[6] an Australian ophthalmologist, who noted that 68 of 78 infants with congenital cataracts were born

of pregnancies complicated by rubella infection, and that 44 had congenital heart disease as well.

Swan, Tostevin, and Black,[7] who studied four series of Australian infants whose mothers were believed to have contracted rubella during pregnancy, in 1946 reported a wide range of congenital defects, among which were bilateral cataracts, heart disease, microcephaly, deaf-mutism, spastic diplegia, mental deficiency, talipes equinovarus, cleft palate, bifid uvula, and high arched palate.

Wesselhoeft[8] summarized the retrospective studies of rubella during pregnancy reported in the literature prior to 1949. Of 780 children from pregnancies complicated by rubella, 124 were normal, 310 had eye defects, 296 had cardiac defects, 281 were deaf, 98 were microcephalic, 79 were mentally retarded, and 22 had been reported to have dental defects. He noted, however, that "...the backward approach to this whole subject renders any mathematical calculation open to serious objection."

Michaels and Mellin[9] in 1946 established more restrictive criteria* for inclusion of cases to be studied but

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*The criteria of Michaels and Mellin were:
"1. The diagnosis of rubella was made and recorded before delivery.
2. The diagnosis of rubella was made by a physician in most cases.
3. At least one careful follow-up examination of the progeny was made in most cases.
4. The timing of maternal rubella is known by week or month of gestation for the fetal deaths, normal live-born infants, and the affected offspring."

collected only a small sample, which led them to combine their data with those of nine other authors.[10,11,12,13,14,15] They concluded that the percentage of children with fetal abnormalities decreased progressively according to the month of gestation in which the mother experienced rubella infection, with incidence of 47 per cent, 22 per cent, and 7 per cent for the first twelve weeks, divided into thirds respectively.

The 1951 epidemic in Sweden was studied by the national health service by means of questionnaires, and Lundstrom[16] compiled the voluminous data which resulted. This prospective study included the analysis of 1,159 children whose mothers had rubella during pregnancy, with 463 of these infants having been affected during the first trimester. The stillbirth and morbidity rates for this group were higher than normal, as was the frequency of spontaneous abortion. A higher incidence of immaturity, subnormal length and birth weight, and retarded functional and physical development was found among the survivors, with a significantly higher incidence of deafness, chorioretinitis, congenital heart disease, and cataracts being noted in these children who were examined at birth and again at ages one and three years. Delayed eruption of

the deciduous teeth was also noted and will be discussed in detail later in this review. The incidence of congenital birth defects was 10 per cent, which gave a confidence level interval of 7 to 17 per cent. Lundstrom noted that in 469 cases which he collected from the literature, the comparable estimate was 16 to 23 per cent, which was statistically significantly higher than the incidence which he had reported.

In a thirteen year (1950-63) study conducted in New York, Tartakow[5] followed a group of 126 female patients with maternal rubella. Of the 87 full-term and 11 premature infants which were born to women in the study group, 17 had congenital malformations which included the "major" defects of cerebral palsy and thrombocytopenia purpura, as well as "...defects related to...dentition."

Of the 31 offspring from the 1955 Montreal epidemic reported by Oxorn,[17] 25 were normal. In 1959, however, Liggins and Phillips[18] found a 34 per cent risk of fetal abnormalities from first trimester rubella in their more stringently supervised study in New Zealand. An apparently even greater virulence of the rubella virus was observed by Siegel and Greenberg[19] in 1960 in reporting 100 per cent incidence of major congenital defects in live births from

exposure to rubella in the first four weeks of gestation during epidemic years.

The following year, Campbell[20] of Guy's Hospital expressed concurrence with the growing use of the term, "rubella syndrome," on noting the unique combination of heart defects observed exclusively among children from rubella-complicated pregnancies. He listed deafness as the most frequently occurring defect, cataracts as the third most likely, and offered the following percentage distribution of the second most likely defect, congenital heart disease:

Patent ductus arteriosus	58 per cent
Ventricular septal defect	18 per cent
Patent ductus and ventricular septal defect	6 per cent
Atrial septal defect	6 per cent
Pulmonary valvar stenosis	6 per cent
Tetralogy of Fallot	6 per cent.

He combined his data with those of other studies in the current literature to assess the relative severity of congenital abnormalities in relationship to the time of contracting maternal rubella. No increase over the normal 2.5 per cent incidence of congenital defects was found when maternal rubella was contracted after the fourth month of gestation.

The concept that the defects of rubella viral etiology might constitute a discrete syndrome was expanded as

additional specialties of medicine adapted their disciplines to diagnostic inquiries based upon the already documented complement of abnormalities caused by maternal rubella. Lindquist and his associates[21] described changes in the long bones noted on radiographic examination of rubella infants; and Rudolph and his co-workers[22] noted that these changes were similar to those observed in such metabolic disturbances as hypophosphatasia and erythroblastosis fetalis, as well as in spirochetal infections such as congenital syphilis. Moreover, they reported the stigma of hepatosplenomegaly.

The first serological studies of children with rubella syndrome were those of Dudgeon, Butler, and Plotkin[23] who studied 31 children with congenital defects following maternal rubella. They concluded that, "...intrauterine infection with rubella virus does not lead to immunological tolerance but is followed by persistence of virus, with subsequent development of active immunity probably by the fetus or early in postnatal life."

Sever, Schiff and Huebner,[4] in testing 600 pregnant women for rubella-neutralizing antibodies, noted that there was no correlation between the reported history of rubella and the presence or absence of antibodies, a finding of

considerable interest to the clinician. Avery and his co-workers[24] found that seven pregnant women who presented with subclinical rubella subsequently delivered babies with "classical features of rubella syndrome" from whom virus was isolated.

Of interest also is the report by Schiff, Smith, Dignan, and Sever[25] of a case of infection with ECHO virus 9 in an employee of the Cincinnati Children's Hospital outpatient clinic. The patient's symptoms were clinically indistinguishable from those of rubella and reportedly most likely would have been diagnosed as such in the absence of antibody titer determinations and daily throat swab cultures.

Weller, Alford, and Neva,[26] in testing for the presence of rubella neutralizing antibody in rubella syndrome, found 4 of 25 control group children under 13 years of age to have rubella antibodies, as contrasted to seropositive findings in 16 of 19 congenitally acquired rubella specimens. These three authors[27] subsequently recovered 38 strains of rubella virus from tissue specimens from the products of conception of 24 of 51 women who had experienced clinical rubella during the first trimester of pregnancy, giving an isolation rate of 47 per cent. In their[28] study

of newborn infants with rubella syndrome, rubella virus was successfully isolated from the throat and the urine of three infants for 10 weeks after birth. The similarity of this finding to the conditions of congenital infection with cytomegalovirus, syphilis, and toxoplasmosis was noted.

Korones and his associates[29] subsequently isolated rubella virus from the liver of each of their 22 patients; and Cooper and his co-workers[30] reported the presence of the virus in "virtually every organ" of the body of infected children. Tondury,[31] describing the specific "organ-affinity" of the rubella virus, states:

> "...whereas not until 222 days after the mother beeing (sic) infected by rubella, the sensory cells of the inner ear and the cells of the enamel organ are visibly destructed (sic).
>
> According to our observations we assume, that the virus attacks the epithelial cells of the lens, the auditory vesicle and the enamel organ in premature embryonic state (sic) and increases therein...."

He notes that changes in the eye are not specifically the unique result of the rubella virus, inasmuch as mumps, infectious hepatitis, and polio also give rise to the same condition.

Since rubella occurs only in monkeys and humans, experimental models of the disease are limited; however, Parkman, Phillips, and Meyer[32] have demonstrated that

rubella virus achieves placental transfer in the Rhesus monkey.

In human embryonic tissue culture experimentation, Plotkin, Boué, and Boué[33] found the rubella virus to arrest mitotic activity, a possibility cited by Naeye and Blanc[34] in their postmorten studies of organs from rubella infants in which the authors attributed the reduced number of cells to intrauterine growth retardation.

In a clinical study of 367 infants with birth weights ranging between three pounds, nine ounces and five pounds, eight ounces, Van den Berg and Yerushalmy[35] of the University of California found that children with a slow intrauterine growth rate (defined as a low birth weight and a normal gestation period) had a higher incidence of anomalies, whereas infants with a fast intrauterine growth rate (defined as a low birth weight and short gestation period) had a neonatal mortality rate which was almost twice that of the other low birth weight children, and moreover seemed to have more difficulty in adapting to the extra-uterine environment. A reversal in this ability to adapt to the environment occurred after the neonatal period (six weeks after birth), with the fast intrauterine growth rate group having fewer illnesses in the first year of life

and "overtaking" the other group in height and weight. The authors emphasized that the rate of intrauterine growth must be determined from both the length of gestation period and the birth weight.

Other authors have been less specific in their definitions of prematurity when studying the relationship of prematurity and dental enamel hypoplasia, even though the accepted definition of birth weight of less than 2,500 kilograms (five and one-half pounds) seems applicable. In their study of 68 premature children, Grahnén and Larsson[36] found that 32 per cent had hypoplasia at five and one-half years of age, whereas 13 per cent of their control group presented with hypoplastic areas of the teeth. The definition of prematurity in this instance was based upon birth weight.

Miller and Forrester[37] examined 99 premature children and found that 46 had hypoplasia, of which 3 had hypoplasia similar to what the authors had seen with kernicterus. They concluded that kernicterus of hemolytic disease and prematurity was always associated with severe enamel hypoplasia. Their judgment of neonatal hypoplasia was based upon the study of ground sections which clearly showed the neonatal line. Their study included intra-oral photographic illustrations depicting premature hypoplasia as consisting

of a smooth ring around the primary cuspid, sharp pointed cusps on the primary molars, and irregular defects of the incisal third of the maxillary anterior teeth.

A similar clinical picture of enamel hypoplasia secondary to prematurity was reported by Stein[38] in a summary of five previous articles written in German. Eight of sixteen prematurely born children had hypoplasia involving the incisal third of the deciduous crowns. Stein emphasized prematurity defined by the length of the period of gestation, although each of his patients weighed less than five and one-half pounds at birth. He described mild cases of enamel hypoplasia as involving only the mesial portion of the incisal edge of the central incisors. In severe cases of hypoplasia, there was a circular thinning of the enamel in the incisal third of the central incisors, cuspids, and the cusps of the molars. By contrast, Stein described hypoplasia due to systemic disorders as "chalky, often stained, and resembling mottled enamel without pits or depressions on the surface." Although his report of 50 per cent of premature children having hypoplasia concurs with Forrester's percentages, Stein did not state whether the children had any difficulty with icterus or whether prenatal complications might have prompted the early delivery of the fetus.

McMillan and Kashgarian[39] also found hypoplasia associated with prematurity, cerebral palsy, and ocular fibroplasia. They studied 286 children in an institution for the mentally retarded and reported that 53.85 per cent of the premature children exhibited enamel hypoplasia. They concluded from their study of forty ground sections of anterior teeth, that all linear hypoplastic defects were neonatal in origin. A subsequent chi-square analysis of the birth weight and position of the linear hypoplasia indicated that as the birth weight decreased, the location of the hypoplasia shifted toward the incisal edge. The authors interpreted generalized enamel defects as an indication of some chronic prenatal influence on the ameloblasts.

Via and Churchill[40] studied 219 two to six year old children with cerebral disorders and concluded that 119 (54 per cent) had enamel hypoplasia. Further, the authors found hypoplasia in 100 per cent of the choreoathetoids and 84 per cent of the spastic diplegics. Milder forms of cerebral disorders such as hemiplegia and focal cerebral seizures were associated with hypoplasia in 38 per cent of the affected children.

Perlstein and Massler[41] studied 250 cerebral palsy children and found 24 per cent to have enamel hypoplasia

of which the authors termed 50 per cent "neonatal" and 50 per cent "prenatal." The criteria for classification of hypoplastic areas as neonatal or prenatal were not defined, however. They also noted that 58 per cent of infants who had suffered kernicterus due to Rh incompatibility had "prenatal" hypoplasia. When the kernicterus had been of non-hemolytic etiology, it was associated with hypoplasia of the enamel in only 22 per cent of the children.

In a study of 120 cerebral palsy children, Herman[42] observed enamel hypoplasia in 36 per cent of the study group, as contrasted to an incidence of 6 per cent in the normal children studied.

Gordon[43] studied 50 cerebral palsy children who had "kernicterus of prematurity" and found 15 (30 per cent) to have enamel dysplasia which was described as chalky areas, pitting and grooving, or aplastic structure of the primary teeth.

Hals and Grahnén[44] in 1965 reported a histologic and microradiographic study of 145 teeth from 80 individuals, of whom 56 had hyperbilirubinemia without hemolytic disease during the neonatal period. They observed no changes in the hard tissue of the primary teeth.

Nelson[45] states that about 80 per cent of children affected with kernicterus develop bilateral choreoathetosis, and that children with kernicterus due to Rh incompatibility are usually mentally retarded and have impaired hearing. He observes, "Kernicterus occurs predominantly in children who are severely jaundiced, especially if they are premature by as little as a week or two...." Thus it appears that the relationship between prematurity, cerebral disorders, kernicterus, and blood dyscrasia cannot yet be defined; and therefore, the etiology of the dental hypoplasia observed in conjunction with these disorders has not been established.

A survey of the literature on the incidence of dental hypoplasia (defined as a clinically observable loss of enamel) of primary teeth in the normal population also revealed inconclusive findings. Via and Churchill[40] reported that 9 per cent of their normal children had hypoplasia of the primary teeth. Grahnén[37] found opaque spots and/or hypoplasia in 13 per cent of children; but Miller and Forrester[38] found no hypoplasia in 105 normal children between one and four years of age.

Barnard[46] reported 42 per cent of 1,200 children three to six years old had opaque areas on at least one

tooth, with 4 per cent having a surface defect or a loss of structure defect on at least one tooth. The lowest figure for hypoplasia in the literature is reported by Pitts,[47] who recorded an incidence of 0.37 per cent, based upon his study of 4,000 primary teeth.

The relationship of cleft lip and palate to dental hypoplasia was explored by Dixon, [48] who compared 76 cleft lip and palate children with 100 normal children and found a higher incidence of hypoplasia in the cleft palate children in all the primary teeth except the mandibular incisors and canines. Mink[49] felt that the hypoplasia of the anterior teeth of cleft palate children was due to surgical trauma of the repair of the cleft lip. In 1966, Kraus[50] presented a more complete report of 39 cleft lip and palate patients. He studied a total of 1,716 teeth from study casts made just after eruption of either the primary or permanent teeth, and reported that 189 (11 per cent) of the teeth had morphologic abnormalities including extra cusp tips and conical shaped anterior teeth.

The most common hereditary defect of enamel is amelogenesis imperfecta, which was classified by Darling[51] as follows:

A. Hypoplastic class
   1. Generalized pitting of enamel
   2. Vertical grooving with wrinkling of enamel surface
   3. Marked deficiency in thickness of enamel

B. Hypocalcified class
   1. Chalky with moderate staining
   2. Badly stained teeth with chipping away of enamel.

In the hypocalcified class, however, Darling noted that there seemed to be a hard layer of enamel next to the dentino-enamel junction. His scheme of classification is included in this study since it is believed to be more applicable to the study of enamel defects than is the system propounded by Sarnat and Schour[52] in 1941.

Delayed eruption of the deciduous dentition has been reported by two authors in their studies of dental conditions associated with rubella embryopathy. Evans[53] was the first dentist to examine children with rubella embryopathy. In 1944 he reported a preliminary study of 34 patients examined in conjunction with the work of Swan, Tostevin, and Black[7] and in 1947[54] published a follow-up study of 67 patients, including those previously reported. He emphasized his findings in 45 children whose mothers had contracted rubella in the first trimester, stating that the defects found in children whose mothers had rubella after the first trimester were "few in number and

minor in degree." The children examined by Evans ranged in age from 12 to 74 months, with an average age of 44.66 months. He noted that 22 children had "delayed eruption," three had congenitally missing teeth confirmed by radiographic examination, 14 had "early caries," and 13 had dental hypoplasia. Generalized hypoplasia was not found. The average number of teeth involved in this group was 3, with 6 being the maximum number. A total of 29 upper and eight lower teeth were hypoplastic, of which 25 were "anterior" and 12 were "posterior." The hypoplasia of 28 teeth occurred in 14 pairs (teeth corresponding to another on the opposite side of the same arch). He reported 8 teeth with abnormal morphology and found 6 children to have a "restricted" arch form. Evans did not comment on this latter finding other than to state that these deviations were not pronounced.

Evans did not compare his rubella group with a control group and did not explain his criteria for classification of the progress of eruption and whether it was delayed. Following the appearance of Evans' first study, the New South Wales Committee[55] questioned Evans' conclusions regarding delayed eruption and first trimester rubella. In a subsequent article he attempted to defend his views

by citing the six cases he had classified as severe delayed eruption. In one child a maxillary second molar erupted at 24 months and his remaining deciduous molars erupted prior to the eruption of the anterior teeth, with the entire set not in evidence until the child was four years old. Although this is an instance of delayed eruption, it could be classified more accurately as a case of anomalous eruption pattern. A second child's first tooth erupted at 13 months and only 10 teeth had erupted by age two and one-half years. According to Meredith's[56] review of the literature, this case would fall within the normal range of age for deciduous tooth eruption.

Meredith's extensive review of the literature prior to 1946 on eruption (with which Evans should have been familiar) raises doubt concerning Evans' conclusion that delayed eruption is in fact characteristic of the rubella syndrome. Although Meredith stated that 90 per cent of children normally have completed eruption by three years of age, he cited reports of individuals lacking the eruption of a full deciduous complement at 36 and 38 months, as well as other "normal" children who did not erupt any teeth until as late as 18 months.

Lundstrom, Lysell and Berghagen[57] in 1962 published

an expanded report of the dental findings from the 1951 epidemic in Sweden. Of the 979 rubella embryopathy cases examined, the authors limited their study of delayed eruption to a group of 292 children aged 13 to 18 months at the time of examination by physicians, and compared this group with 358 control subjects who had no medical problems. The rubella group children had a statistically significantly smaller number of teeth in a comparison of the average number of teeth per patient for each group. No correction was made for the effects of prematurity, presumably because rubella syndrome is reported to be characterized by a gestation period of normal length accompanied by low birth weight of the offspring. No correlation was found between the rubella patients' length or weight at birth, or head circumference at the time of examination, and delayed eruption.

In subsequent examinations conducted by a dentist, 55 of these 292 rubella children were found to have no dental hypoplasia at five years of age. This group was subdivided according to month of gestation at the time of maternal rubella, as follows,

Number of Children	Time of Rubella
35	First four months of gestation
20	Four to eight months of gestation

and was compared with a control group of 33 normal children.

Enamel hypoplasia was not found, even among the normal control group children, and the incidence of missing and carious teeth between groups was not statistically different. In data compiled from the dental histories of the 33 children from pregnancies complicated by rubella during the first four months of gestation, the time of eruption of the first deciduous tooth was not statistically different from the times reported for either the control group or for the group of children from pregnancies complicated by rubella during the second four-month period.

In 1958, Grahnén[58] reported his findings from the clinical examinations of a mixed group of 21 children, namely, 12 children between four and five years old, and 9 children from Lundstrom's study that were "about three years old." Although the children were reported to be the products of rubella complicated pregnancies, only one child (thought to have congenital heart disease) in the group of 21 was not in good health. The deciduous teeth of two girls presented symmetrical hypoplasia and one boy had an "isolated opaque area of enamel," for a total incidence of hypoplasia of 14.3 per cent for the 21 rubella children. Grahnén used the figures for the incidence of delayed eruption in the control group from his previously

examined normal children (studied in comparison to premature children) and found no delayed eruption. Although caries was reported, Grahnén did not compare its incidence with that of caries in a control group and therefore could not accurately state its incidence in this group of children.

Raison, Lepoivre and Chatillon,[59] in 1954, reported the results of a dental study of 15 children born of mothers who had rubella in the first three months of gestation. All the children had congenital defects which have been reported to occur subsequent to *in utero* infection with rubella. Although the authors reported that the incidence of dental defects was no higher than normal, they pointed out that the sample was too small to draw any conclusions. The age range of the children studied was wide enough to include both children with primary teeth only and children with all of their permanent teeth.

Current investigators, including Kraus and Jordan[60] and Nomata,[61] have shown that certain previously accepted concepts of tooth development are incorrect and that the past research which was based upon the mistaken ideas is of limited value. The work of early dental scientists who relied upon Logan and Kronfeld,[62] Massler and Schour,[63]

Gottlieb,[64] and others for explanation of experimental findings must now be re-evaluated in the light of this new data. A brief discussion of certain recent studies of the formation, eruption, and morphology of the primary teeth is therefore appropriate.

The average time and sequence of initiation of calcification of the deciduous teeth as presented by Kraus and Jordan[60] is as follows:

1.	Central incisors	14 weeks in utero
2.	First molars	15 1/2 weeks in utero
3.	Lateral incisors	16 weeks in utero
4.	Cuspids	17 weeks in utero
5.	Second molars	18 weeks in utero

It was observed that the primary incisor may start to calcify as early as 12 weeks or as late as 16 weeks, but that the sequence remains constant despite individual variations in initiation and completion of calcification. The authors note, "...it can only be said that in the case of the incisors and first molar, the maxillary tooth precedes its mandibular antagonist."

Kraus and Jordan describe the primary molars at birth as having almost complete union of each calcification center. They note, "The conical appearance of the cusps and the lack of distinctive details of the occlusal surface indicate that considerable deposition of enamel is yet to occur before calcification is complete." They do not state

to what extent the calcification of the anterior teeth has progressed at birth because the essential morphology of these teeth does not change with increased deposition of new enamel as does the cusp tip of the molar. They assert, "The increase in size of the molar crown is a function of mitotic activity in the inner enamel epithelium."

The morphology of the anterior teeth is developed from a conical or "hemispherical mound-like structure." At this stage of early morphologic differentiation, the three anterior teeth are not mutually distinguishable. At about 13 weeks in utero, the central incisor changes by increasing in size and developing an elevated mesial and distal portion at the incisal edge. The lateral incisor differs in that the distal portion does not usually develop the same prominence as it does in the central, whereas the cuspid develops without great change from the conical morphology.

The literature on tooth eruption was reviewed again in 1964 by Lysell, Magnusson, and Thilander.[65] They observed that "deviation from the reported normal order of eruption was the rule and not the exception," and that sex differences, large individual variations in the period of time

between the eruption of the first tooth and the completion of eruption, and differences in eruption between left and right sides of the jaws had been reported. In 1959, Garn, Lewis, and Polacheck[66] studied 255 Ohio children and stated that the range of normal eruption of the primary teeth was about three times as long as what is generally quoted.

The age of the patient with rubella embryopathy at the time of examination assumes significance in the light of a study by Giles, Cooper and Krugman[67] who noted that only 17 of 69 anomalies seen at age five had been observed at birth. Thus it may be that the entire effect of the 1964 epidemic of rubella will be revealed only as time passes, and the children infected in utero at that time as part of the estimated 1,800,000 cases[68] can be studied more completely.

STATEMENT OF PROBLEM

It is well known that a child infected *in utero* with rubella may have the characteristic defects of the eye, ear, and/or heart known as rubella embryopathy, which in its expanded syndrome also includes neonatal jaundice, thrombocytopenia purpura, hepatosplenomegaly, and bone lesions. It has been observed that virtually every organ may be infected in a child who has rubella embryopathy.

Although the effect of rubella embryopathy on most organ systems has been previously documented, the effect of the rubella virus on the dental organ has not been adequately evaluated. In fact, the clinical studies reported have been contradictory as to the effect of rubella on the dentition. Only one histologic study has suggested the possibility of any direct effect of the virus on the tooth substance as a result of damage to the enamel organ.

The present study is designed to test for the presence of clinically demonstrable dental abnormalities in children with rubella embryopathy. By evaluating the resultant data in light of their medical histories, this study hopes to provide some specific information about the effect of rubella upon the development of the primary dentition.

MATERIALS AND METHODS

The study group was chosen from children born between July 1, 1964, and July 1, 1965. These children had been examined at the Indiana University Medical Center and were found to have congenital heart disease or a hearing loss due to their mother's reported exposure to rubella or an actual infection with rubella during the pre-natal period. A letter was sent to the parents or guardian of each child requesting their participation in the study, and a return postcard was provided for their reply. Families living in the Indianapolis area were contacted by telephone for their reply. Appointments were scheduled for each participating child to be examined at the James Whitcomb Riley Hospital for Children Dental Clinic. Arrangements were made for an examination in their home or elsewhere at their request when they were unable to travel to the Medical Center. A total of 50 patients born between September, 1964, and February, 1965, were examined between June 8, and December 6, 1967. Nine children were seen in private homes, 37 at the James Whitcomb Riley Hospital for Children Dental Clinic, and four patients were examined at the Rehabilitation Center in Evansville, Indiana.

At the time of examination, a verbal history was

recorded as related by the patient's mother or other accompanying adult, who was questioned specifically about illness or complications and medications taken during the pregnancy. The questions emphasized the manifestations of the mother's rubella infection or exposure. The mothers were asked to relate any medications taken by the child, and any illness or surgery he had experienced. The family history was explored for the incidence of physical abnormalities as well as unusual dental conditions. The information which was obtained from each individual interview was recorded on a history sheet (Figure 1) which was subsequently abbreviated (Figure 2) for the history interviews with the mothers of the control group children.

Following each interview, a complete dental examination was performed, using a dental light, mirror, and explorer, and the findings were recorded on an examination form (Figure 3). Abnormalities of the gingivae, palate, oral soft tissue, facial skeleton, and occlusion were noted. Any non-carious defect of the enamel surface which could be detected with the explorer was recorded as "enamel hypoplasia." Any white area (as contrasted to normal translucent enamel) was recorded as "enamel opacity."

Abnormalities of tooth morphology were recorded as "abnormal shape," unless they were attributed to enamel hypoplasia, in which case they were recorded as "hypoplasia." The approximate size, shape, and location of these areas were sketched on the schematic diagram of the teeth on the examination form (Figure 3) according to the key listed thereon.

Intra-oral and full-face 33mm. Kodachrome and Ektachrome photographs of 48 children were taken with a Coret Speed camera, and 127 mm. Kodachrome slides and Kodacolor photgraphs were taken of two children, respectively. Radiographs and study cast impressions were not attempted because of the immaturity of the patients.

A hand light was substituted for the dental light for 13 examinations not performed in the James Whitcomb Riley Hospital for Children Dental Clinic.

Measurements of each child's height, weight, and head circumference were made in the manner described on the Boston Children's Medical Center Anthropometric Chart (Figure 4). The weight of those children seen at home was estimated by the mother when scales were not available, and was subsequently checked for accuracy by comparing it with the weight recorded in the child's medical chart at

the time of his most recent visit to the Medical Center.

Two children were being cared for in foster homes. The only available source of pre-natal history in these cases was the child's Medical Center record, which in one instance was supplemented by the physical findings recorded by attending physicians at the Suemma Coleman Home in Indianapolis.

The Indiana University Medical Center charts were examined in all 50 study cases to confirm the mother's verbal history; and in two instances there was a discrepancy of reported birth weight between the interview and the record, whereupon the weight recorded most recently after the birth was assumed to be more correct. In all the study cases the diagnoses of medical abnormalities were made by a physician, and all but three of the diagnoses of cardiac defects had been confirmed by cardiac catheterization.

A control group of 50 apparently normal children born between May, 1964, and March, 1966, was selected at random from the population of two to three year old children seen at the neighborhood welfare clinics of the Marion County Health and Hospital Corporation. All children in the control group were examined between October 1, 1967,

and January 30, 1968. The group consisted of 25 boys and 25 girls. Measurements of height were not made for this control group, but in all other respects their interviews and examinations were performed in the same manner as those of the study group.

RESULTS

The basic medical data collected from the study group of 50 children (average age at examination, 30.8 months) whose sex distribution was 29 females and 21 males, are presented in Tables I and II and are summarized in Tables IV and V. Each child in the study group had at least one congenital defect associated with *in utero* rubella infection.

Of the 44 children who demonstrated a loss of hearing confirmed by the Indiana University Medical Center Department of Audiology and Speech, 15 had no other medical abnormality associated with rubella embryopathy at the time of examination.

Of the 28 children with congenital heart disease, only three had no other medical abnormality. Patent ductus arteriosus was the most common cardiac disease, occurring as an isolated heart defect in four children and in combination with other cardiac defects in 13 others. The second most common heart defect was pulmonary stenosis, which accompanied patent ductus arteriosus in nine children and occurred as an isolated heart defect in three children. Additional cardiac abnormalities included ventricular septal defect, coarctation of the aorta, supravalvar aortic stenosis, and dextrocardia.

Nineteen children had eye defects, including 11 with

cataracts, four with salt and pepper retinopathy, two with glaucoma, and one each with chorioretinitis and strabismus.

Additional medical findings included the incidence of two cases of cerebral palsy and one case of juvenile diabetes.

The control group of 50 children consisted of 25 females and 25 males whose average age at examination was 30.9 months (Table III).

The comparisons of the averages of the birth weights, weights at time of examination, length of period of gestation, age at examination in months, and the standard deviations for these variables are as follows:

	Birth Weight	Gestation in Weeks	Age at Examination in Months	Weight at Examination
Study Group	6.16 lbs. S.D.=1.22	39.20 S.D.=2.28	30.84 S.D.=3.41	24.78 lbs. S.D.=4.46
Control Group	7.02 S.D.=1.38	39.66 S.D.=2.03	30.89 S.D.=5.75	29.60 lbs. S.D.=3.97

Forty-five (90 per cent) of the children in the study group had enamel hypoplasia, whereas 13 children (26 per cent) in the control group had enamel hypoplasia. The average number of hypoplastic teeth per child in the study group was 6.64, as contrasted to 1.92 teeth per child in the control group. The most frequently affected tooth in the study group was the maxillary central incisor, which

was hypoplastic in more than 50 per cent (26 individuals) of the children (Table VIII). The lower cuspids were the teeth most commonly affected by hypoplasia in the control group.

Two types of abnormalities of shape other than those due to hypoplasia were noted. Seventy-eight per cent of the children in the study group had at least one anterior tooth with a constricted or tapered incisal third (Figures 5 and 6) as determined subjectively on the basis of previous clinical experience. Eighteen per cent of the children in the control group were judged to have tapered anterior teeth. The average number of tapered teeth per child in the study group was 3.85, as contrasted to an average of 2.33 tapered teeth per child in the control group. The lower right lateral incisor was tapered in 26 of the study group children (Table X). The cuspids of the control group children were judged to be more tapered than normal.

A notching of the incisal edge of the anterior teeth was the second defect of non-hypoplastic origin noted in the study group, and was not related to a history of trauma in any instance. Fifteen notched teeth, of which 11 were maxillary and four were mandibular, were noted in the study group (Table XI). One child had a total of three such teeth (Figure 7).

Dental caries was present in only one child of the study group and in only one child in the control group.

No clinically observable abnormalities of the tongue, cheeks, mandible, maxilla, or gingivae were noted in either the study group or the control group, except for one child with a cleft of the lip and palate in the study group.

In the assessment of progress of tooth eruption, each tooth was recorded as either "present" or "not present," depending upon whether any portion of the tooth was clinically observable (Table VII). The average number of such observable teeth per child in the study group was 17.40, whereas the average number per child in the control group was 18.22 teeth.

The following statistical analysis of the data was prepared by Dr. Rosario H. Y. Potter of the Departments of Medical Genetics and Pedodontics, Indiana University Medical Center, Indianapolis. The computations for this project were performed at the Indiana University Medical Center Research Computation Center, which is supported in part by Public Health Service Research Grant Fr 00162-03.

For statistical analysis the children in each group were divided by sex so that not only the differences

between the study and control groups but also the presence of differences in the data for each sex group could be tested. For binomial data (number of children with hypoplasia, tapered teeth, and notched teeth) a chi-square test was used for the analysis of the differences between the two groups. In the analysis of the variables of weight at time of examination, length of time of gestation, birth weight, and number of teeth examined, a 2 x 2 factorial design was used to test for male and female interaction. The F test was used to find the probability.

Because many of the children had incompletely erupted primary teeth, the number of teeth that were hypoplastic, tapered, or pointed were compared with the number of teeth examined in each individual. This proportion was transformed into angular data for analysis and, therefore, the numerical results included here are abstractions from the data and are suitable for use only for the statistical analysis of this proportion. The F test was used to find the probability.

Table V summarizes the analysis for the variables of age and weight at examination, length of gestation period, birth weight, and number of teeth examined. There was no significant difference between the control group and the

study group with respect to age at examination, gestation period, or number of teeth erupted. There was a significant difference in the birth weight and weight at examination between the study and control groups ($p < .005$).

Table IX summarizes the analysis of the hypoplastic defects. Nineteen of 21 males and 16 of 19 females in the study group had hypoplastic teeth. In the control group 4 of 25 males and 9 of 25 females had hypoplastic defects of the primary teeth. The chi-square analysis of the number of children with enamel hypoplasia showed a significant difference between the groups ($p < .005$) and between the sexes ($p < .05$). Since in both the study and the control group the females had a higher incidence of hypoplasia, the interaction was not significant.

Table IX summarizes the analysis of the data concerning tapered teeth. Seventeen of 21 males and 22 of 29 females in the study group had tapered teeth. In the control group, 3 of 25 males and 6 of 25 females had tapered teeth. Although there was no difference between the sexes nor an interaction with respect to the number of children with tapered teeth, there was a statistical difference ($p < .005$) between the control group and the rubella group. In analyzing the transformed data for the proportion of tapered

teeth to examined teeth in each individual, a significant interaction ($p<.005$) was found between the males and females. Separate analysis of the data for each sex gave a t test for the males of 6.648 and a t test for the females of 4.114 ($p<.005$). This showed that both the females and the males in the study group had a significantly greater proportion of tapered teeth to erupted teeth than did the control group.

Because none of the children in the control group had notched teeth, the interaction between the sexes could not be calculated. The t test for the proportion of notched teeth to total erupted teeth in each individual in the study group was 3.218, which is statistically significant ($p<.005$).

TABLES

TABLE I

AGE AND WEIGHT AT EXAMINATION AND MEDICAL DIAGNOSIS FOR THE STUDY GROUP

NAME	AGE (months)	WEIGHT (lbs.)	DEFECTS OF: HEARING	HEART	EYE	OTHER
A.A.	30.00	21.00	+			
S.A.	42.50	36.00	+	+		Mental retardation
K.A.	32.75	29.00	+	+		
C.B.	30.50	20.00	+	+		Foot deformity Feeding problem
C.B.	33.50	32.00	+			Cerebral palsy Motor retardation
W.B.	31.75	28.75	+			
T.B.	29.75	26.00	+	+	+	Microcephaly Thrombocytopenia
P.B.	33.50	27.00	+		+	Cerebral palsy Microcephaly
P.B.	28.75	27.75		+		
S.B.	32.25	29.00	+			
S.C.	18.25	17.50	+	+	+	Microcephaly Feeding problem
J.C.	29.75	31.00		+		
D.C.	30.50	21.50	+		+	Mental retardation Motor retardate
D.C.	28.75	22.00	+	+	+	Motor retardate
C.D.	30.50	26.00		+	+	Microcephaly

TABLE I
(continued)

NAME	AGE (months)	WEIGHT (lbs.)	DEFECTS OF: HEARING	HEART	EYE	OTHER
L.D.	33.50	27.00	+			
M.D.	31.50	27.50	+			
B.F.	29.75	18.00	+	+		Microcephaly Mental retardation
D.G.	35.00	28.50	+			
L.G.	30.00	22.50	+		+	Mental retardation Motor retardate
M.H.	28.00	24.00	+	+		Microcephaly
D.H.	30.75	20.50	+		+	Mental retardation
K.H.	30.00	24.00		+	+	Mental retardation Feeding Problem
B.J.	28.25	15.00	+	+	+	Mental retardation Microcephaly
K.K.	31.00	17.75	+	+	+	Mental retardation
D.L.	32.00	29.50	+			
J.L.	34.50	27.25	+	+		
W.L.	33.25	29.00	+			
G.L.	31.50	25.00	+	+	+	
N.L.	30.00	21.00	+	+		
J.L.	30.50	18.50		+		Mental retardation Motor retardate
M.L.	30.50	24.00		+	+	Motor retardation

TABLE I
(continued)

NAME	AGE (months)	WEIGHT (lbs.)	DEFECTS OF: HEARING	HEART	EYE	OTHER
C.M.	31.50	26.00	+			
J.M.	33.25	26.00	+		+	
J.O.	29.25	27.00	+	+		Microcephaly Icterus
T.P.	32.50	28.00	+			
L.P.	32.00	28.00	+	+	+	Diabetic Motor retardation
J.R.	28.50	22.50	+		+	Foot deformity
D.S.	33.25	33.50	+			
M.S.	36.75	23.00	+	+		Supravalvar aortic stenosis
S.S.	31.00	22.00	+		+	Mental retardation Motor retardate
R.S.	31.50	25.00	+	+		Cleft lip and palate
L.T.	27.75	21.00	+	+		Microcephaly
J.T.	30.00	16.00	+	+	+	Mental retardation Microcephaly
W.T.	21.00	22.00	+			
P.T.	32.75	27.00	+			
V.V.	30.00	24.00	+			Mental retardation Motor retardate
T.W.	30.00	24.00	+	+		Icterus Thrombocytopenia
D.W.	29.00	27.75	+	+	+	Mental retardation Foot deformity
S.W.	29.00	23.00	+	+		

TABLE II

GESTATION, BIRTH WEIGHT, TIME OF RUBELLA AND THE DENTAL DEFECTS IN THE STUDY GROUP

NAME	SEX	LENGTH OF GESTATION (weeks)	BIRTH WEIGHT (lbs.)	RUBELLA (weeks) (in utero)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH	NOTCHED TEETH
A.A.	F	41	6.81	6	20	6	4	3
S.A.	F	43	7.50	0	20	2	0	0
K.A.	F	42	8.65	10	20	1	4	0
C.B.	F	43	4.62	0	15	6	2	0
C.B.	F	40	6.94	14	20	5	0	2
W.B.	M	39	6.75	6	20	1	2	0
T.B.	M	33	4.62	6	20	17	5	1
P.B.	M	36	5.94	14	14	1	2	0
P.B.	M	40	9.19	1	20	0	0	0
S.B.	M	41	6.62	12	20	4	0	0
S.C.	F	40	5.62	6	7	2	0	0
J.C.	M	40	8.69	6	19	8	2	0

TABLE II
(continued)
GESTATION, BIRTH WEIGHT, TIME OF RUBELLA AND THE DENTAL DEFECTS

IN THE CHILDREN WITH RUBELLA EMBRYOPATHY

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	RUBELLA (weeks) (in utero)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH	NOTCHED TEETH
D.C.	M	34	4.31	?	10	9	4	1
D.C.	M	40	5.87	3	16	2	2	1
C.D.	F	40	5.19	6	20	3	1	0
L.D.	F	40	8.50	9	20	5	2	0
M.D.	F	42	6.19	12	16	3	0	0
B.F.	F	36	4.87	10	16	9	0	0
D.G.	M	37	5.00	3	20	1	0	0
L.G.	F	40	5.44	6	15	8	1	0
M.H.	F	34	5.81	4	20	3	4	0
D.H.	F	41	5.75	4	16	7	2	0
K.H.	F	40	6.62	2	17	11	4	0
B.J.	F	36	5.81	10	14	2	2	0

TABLE II
(continued)
GESTATION, BIRTH WEIGHT, TIME OF RUBELLA AND DENTAL DEFECTS

IN THE CHILDREN WITH RUBELLA EMBRYOPATHY

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	RUBELLA (weeks) (in utero)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH	NOTCHED TEETH
K.K.	M	40	4.19	1	20	8	3	0
D.L.	F	39	6.75	12	20	0	0	0
J.L.	M	38	6.31	4	20	11	5	2
W.L.	F	41	7.13	5	20	2	1	0
G.L.	M	40	6.25	10	18	18	5	0
N.L.	F	40	5.75	4	20	3	1	2
J.L.	M	42	5.87	8	16	14	6	0
M.L.	M	39	5.19	10	13	11	6	0
C.M.	M	41	6.13	3	20	10	4	0
J.M.	F	40	6.69	6	18	10	6	0
J.O.	M	38	5.19	10	13	11	7	0
T.P.	M	40	6.69	7	20	0	0	2
J.P.	F	40	7.06	4	20	11	6	1

TABLE II
(continued)
GESTATION, BIRTH WEIGHT, TIME OF RUBELLA AND THE DENTAL DEFECTS

IN THE CHILDREN WITH RUBELLA EMBRYOPATHY

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	RUBELLA (weeks) (in utero)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH	NOTCHED TEETH
J.R.	M	38	5.56	3	20	11	2	0
P.S.	F	40	8.69	11	20	0	2	0
M.S.	F	40	5.31	?	18	0	6	0
S.S.	M	36	5.62	8	20	9	8	0
R.S.	F	40	8.00	8	16	8	4	0
L.T.	F	36	4.75	0	11	10	2	0
J.T.	F	36	4.13	6	8	6	2	0
W.T.	M	38	5.50	6	20	6	2	0
P.T.	M	40	6.81	8	16	4	4	0
V.V.	F	40	6.31	12	20	12	3	0
T.W.	F	42	5.00	7	18	2	2	0
D.W.	F	38	5.37	4	14	3	0	0
S.W.	F	40	6.31	6	16	3	1	0

TABLE III

DISTRIBUTION OF VARIABLES FOR THE CHILDREN IN THE CONTROL GROUP

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	AT EXAMINATION AGE (months)	AT EXAMINATION WEIGHT (lbs.)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH
R.B.	F	40	6.31	27.25	26.50	16	0	0
M.B.	M	37	6.25	39.50	30.75	20	0	0
L.B.	F	42	9.40	23.50	29.00	10	2	0
C.B.	M	40	8.00	36.50	35.00	20	0	1
V.B.	F	40	6.72	20.75	26.00	16	0	0
T.B.	M	40	6.44	30.50	27.50	20	0	0
K.B.	F	40	6.50	34.75	31.00	20	1	0
C.B.	F	40	6.00	30.00	24.00	20	0	0
J.E	M	37	6.44	26.50	32.00	18	0	0
D.F.	M	44	7.65	30.50	25.00	16	4	2
J.F.	M	42	7.16	30.50	33.50	16	0	0
L.G.	F	40	6.56	32.75	28.00	20	1	0
R.G.	M	40	8.56	41.50	33.50	20	0	0

TABLE III
(continued)
DISTRIBUTION OF VARIABLES FOR THE CHILDREN IN THE CONTROL GROUP

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	AT EXAMINATION AGE (months)	AT EXAMINATION WEIGHT (lbs.)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH
E.H.	F	40	8.25	39.25	35.75	20	0	0
S.H.	F	36	6.94	35.25	27.25	20	1	4
K.H.	F	40	5.97	35.25	24.00	12	0	0
P.H.	F	40	7.34	25.00	29.00	16	2	2
P.H.	F	37	3.00	34.50	31.50	20	4	0
D.H.	M	38	5.00	35.50	31.25	20	0	0
M.H.	M	40	7.37	30.75	30.75	20	0	0
T.H.	F	40	7.19	24.25	24.75	16	1	0
R.K.	M	36	4.00	31.50	32.00	20	0	2
K.K.	M	40	8.87	27.25	33.00	20	0	0
C.L.	M	40	7.44	37.25	29.50	16	0	0
C.L.	M	39	7.31	24.25	25.00	16	0	0
R.L.	F	40	9.13	36.00	28.00	20	0	0

TABLE III
(continued)
DISTRIBUTION OF VARIABLES FOR THE CHILDREN IN THE CONTROL GROUP

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	AT EXAMINATION AGE (months)	AT EXAMINATION WEIGHT (lbs.)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH
K.L.	M	39	6.94	29.25	28.00	20	0	0
M.L.	F	36	6.00	26.00	28.50	20	0	0
R.M.	F	46	7.84	28.25	30.00	20	0	0
D.M.	M	40	9.00	25.50	29.75	16	0	0
M.M.	F	40	6.42	23.25	32.00	16	0	5
G.M.	F	41	4.69	31.25	27.75	20	2	2
B.M.	F	40	5.50	25.75	29.25	16	0	0
S.M.	M	42	8.13	24.75	28.75	16	0	0
C.M.	M	36	5.69	26.75	27.25	19	0	0
S.M.	M	42	7.37	29.00	28.00	20	0	0
J.P.	M	41	6.19	39.50	41.00	20	4	0
J.P.	M	40	7.84	23.50	27.75	20	1	0

TABLE III
(continued)
DISTRIBUTION OF VARIABLES FOR THE CHILDREN IN THE CONTROL GROUP

NAME	SEX	GESTATION (weeks)	BIRTH WEIGHT (lbs.)	AT EXAMINATION AGE (months)	AT EXAMINATION WEIGHT (lbs.)	TEETH ERUPTED	HYPOPLASTIC TEETH	TAPERED TEETH
J.P.	M	36	6.31	31.25	27.50	16	0	0
L.R.	M	40	7.72	25.00	26.50	18	0	0
P.R.	F	40	7.56	36.25	33.50	20	0	0
G.S.	F	40	7.44	28.25	28.25	20	0	0
J.S.	M	38	10.00	31.00	30.50	14	1	0
M.S.	F	36	5.37	35.25	33.50	20	1	0
S.S.	F	40	6.62	23.50	20.00	16	0	2
T.T.	F	40	5.69	32.25	26.00	20	0	0
J.V.	M	40	8.69	39.50	36.00	20	0	0
K.W.	F	40	7.31	41.00	28.00	20	0	0
R.W.	F	40	8.50	42.75	40.50	20	0	1
R.W.	M	42	8.25	24.25	28.00	16	0	0

TABLE IV

DISTRIBUTION OF PHYSICAL ABNORMALITIES IN CHILDREN WITH RUBELLA EMBRYOPATHY

NUMBER OF CHILDREN	GENERAL ABNORMALITIES	SPECIFIC ABNORMALITIES	NUMBER OF CHILDREN
44	HEARING	DEAF	33
		HEARING LOSS	11
28	HEART	PATENT DUCTUS ARTERIOSUS	17
		PULMONARY STENOSIS	14
		VENTRICULAR SEPTAL DEFECT	4
		HEART MURMUR	4
19	EYE	CATARACTS	11
		RETINOPATHY	4
		GLAUCOMA	2
	OTHER	MENTAL RETARDATION	14
		MOTOR RETARDATION	10
		MICROCEPHALY	9
		FEEDING PROBLEM	5

TABLE V

MEAN, STANDARD DEVIATION, AND STATISTICAL ANALYSIS

FOR THE VARIABLES IN THE STUDY AND CONTROL GROUPS

VARIABLE		RUBELLA MEAN	RUBELLA S.D.	CONTROL MEAN	CONTROL S.D.	COMPARISON	F TEST	PROBABILITY
Age at Examination (months)		30.84	3.41	30.90	5.75	Between groups	0.12	n.s.
Length of Gestation (weeks)	Male	38.57	2.31	39.56	2.08	Between groups	1.60	n.s.
						Between sexes	2.21	n.s.
	Female	39.65	2.19	39.76	2.00	Interaction	1.05	n.s.
Birth Weight (lbs.)	Male	6.01	1.24	7.30	1.33	Between groups	11.32	p .005
						Between sexes	0.39	n.s.
	Female	6.26	1.22	6.73	1.39	Interaction	2.47	n.s.
Weight at Examination (lbs.)	Male	25.17	3.57	30.31	3.68	Between groups	31.28	p .005
						Between sexes	1.51	n.s.
	Female	24.51	5.05	28.88	4.18	Interaction	0.21	n.s.
Number of Teeth Erupted	Male	17.85	3.09	18.28	2.03	Between groups	1.60	n.s.
						Between sexes	0.58	n.s.
	Female	17.08	3.62	18.16	2.82	Interaction	0.31	n.s.

S.D. = Standard deviation n.s. = not significant

TABLE VI

DISTRIBUTION OF DENTAL DEFECTS IN THE STUDY AND CONTROL GROUP

	RUBELLA GROUP		CONTROL GROUP	
	Total Number	Average* Number Per Child	Total Number	Average* Number Per Child
ERUPTED TEETH	870	17.40	911	18.22
HYPOPLASTIC TEETH	299	6.64	25	1.92
TAPERED TEETH	131	3.85	21	2.33
NOTCHED TEETH	15	1.67	0	0.00

* These figures were obtained by dividing the number of teeth involved by the number of individuals with the defect.

TABLE VII

DISTRIBUTION AND LOCATION

OF UNERUPTED TEETH

IN FIFTY RUBELLA CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
22	1	7	1	0	0	3	7	0	24	MAXILLA
20	1	9	3	0	0	4	9	1	21	MANDIBLE

DISTRIBUTION AND LOCATION

OF UNERUPTED TEETH

IN FIFTY CONTROL CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
19	0	3	0	0	0	0	3	0	19	MAXILLA
20	0	4	1	0	0	1	4	0	19	MANDIBLE

TABLE VIII

PERCENTAGE DISTRIBUTION*
OF ENAMEL HYPOPLASIA
IN THE RUBELLA CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
29	24	42	40	52	52	40	42	32	19	MAXILLA
30	44	27	21	14	14	20	26	50	29	MANDIBLE

PERCENTAGE DISTRIBUTION*
OF ENAMEL HYPOPLASIA
IN THE CONTROL CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
3	4	2	2	4	2	0	8	2	0	MAXILLA
0	2	9	0	0	0	0	11	2	0	MANDIBLE

* These figures were obtained by dividing the number of teeth involved by the number of teeth examined.

TABLE IX

STATISTICAL ANALYSIS OF THE DATA FOR ENAMEL HYPOPLASIA

NUMBER OF CHILDREN WITH ENAMEL HYPOPLASIA

COMPARISON	CHI SQUARE	PROBABILITY
Among the sample	48.112	$p<.005$
Between the groups	42.036	$p<.005$
Between the sexes	5.911	$p<.05$
Interaction	0.164	n.s.

PROPORTION OF HYPOPLASTIC TEETH
TO
TOTAL TEETH FOR EACH INDIVIDUAL

(Transformed Data)

	RUBELLA		CONTROL	
	Mean	S.D.	Mean	S.D.
MALE	0.70	0.44	0.06	0.15
FEMALE	0.55	0.31	0.11	0.16

COMPARISON	F TEST	PROBABILITY
Between the groups	90.173	$p<.005$
Between the sexes	0.75	n.s.
Interaction	3.112	n.s.

S.D. = STANDARD DEVIATION

n.s. = not significant

TABLE X

PERCENTAGE DISTRIBUTION*

OF TAPERED TEETH

IN THE RUBELLA CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
0	0	5	32	44	40	30	7	0	0	MAXILLA
0	0	0	55	4	4	48	0	2	0	MANDIBLE

PERCENTAGE DISTRIBUTION*

OF TAPERED TEETH

IN THE CONTROL CHILDREN

RIGHT					LEFT					
E	D	C	B	A	A	B	C	D	E	
0	0	4	4	0	0	4	6	0	0	MAXILLA
0	0	9	6	0	0	4	9	0	0	MANDIBLE

* These figures were obtained by dividing the number of teeth involved by the number of teeth examined.

TABLE XI

STATISTICAL ANALYSIS OF THE DATA FOR TAPERED TEETH

NUMBER OF CHILDREN WITH TAPERED TEETH

COMPARISON	CHI SQUARE	PROBABILITY
Among the sample	38.782	$p<.005$
Between the groups	36.058	$p<.005$
Between the sexes	2.564	n.s.
Interaction	0.160	n.s.

PROPORTION OF TAPERED TEETH TO TOTAL TEETH FOR EACH INDIVIDUAL

(Transformed Data)

	RUBELLA		CONTROL	
	Mean	S.D.	Mean	S.D.
MALE	0.41	0.25	0.04	0.10
FEMALE	0.30	0.21	0.09	0.18

COMPARISON	F TEST	PROBABILITY
Between the groups	58.953	$p<.005$
Between the sexes	0.391	n.s.
Interaction	4.396	$p<.05$

S.D. = STANDARD DEVIATION

n.s. = not significant

TABLE XII

DISTRIBUTION AND LOCATION

OF NOTCHED INCISORS

IN FIFTY RUBELLA CHILDREN

RIGHT		LEFT		
B	A	A	B	
2	3	2	5	MAXILLA
0	1	1	2	MANDIBLE

FIGURES

Figure 1

The history interview record sheet.

RUBELLA EMBRYOPATHY

Informant_____

Birth weight_____Gestation_____

Rubella infection: time_____

Delivery: Mother's age_____

Medication during pregnancy: Diet:

Family history:

CHILD
Medications:

Illness:

Surgery:

Review of systems:

eye heart

ear neurological

X-ray interpretation: Clinical laboratory:

Remarks:

Figure 2

The abbreviated history interview sheet.

CONTROL

NAME _____ Date _____

Birth Weight _____ Birth Date _____ Mother's Age _____

Gestation _____ Present Weight _____ First Tooth _____

Pregnancy:

Delivery:

Family History:

Child
Medications:

Illness:

Remarks:

DENTAL FINDINGS:

Figure 3

The dental examination record sheet.

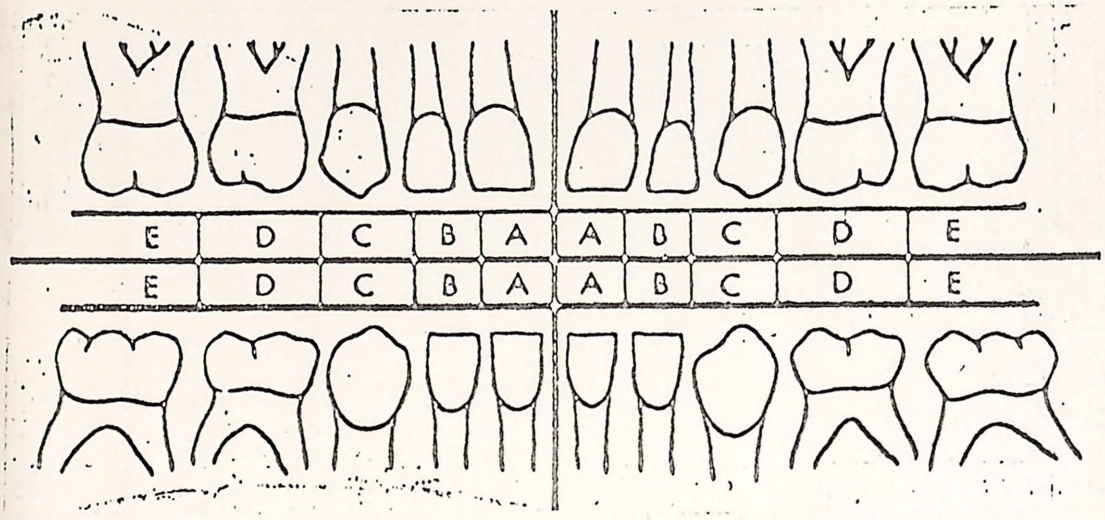
RUBELLA EMBRYOPATHY

Date_____ Age_____ Height_____

Weight_____ Head Circumference_____

First tooth erupted_____

TEETH



Hypoplasia

=Opaque

=Tooth loss

TONGUE

PALATE

LIPS & CHEEKS

GINGIVAE

MANDIBLE & MAXILLA

OCCLUSION

REMARKS

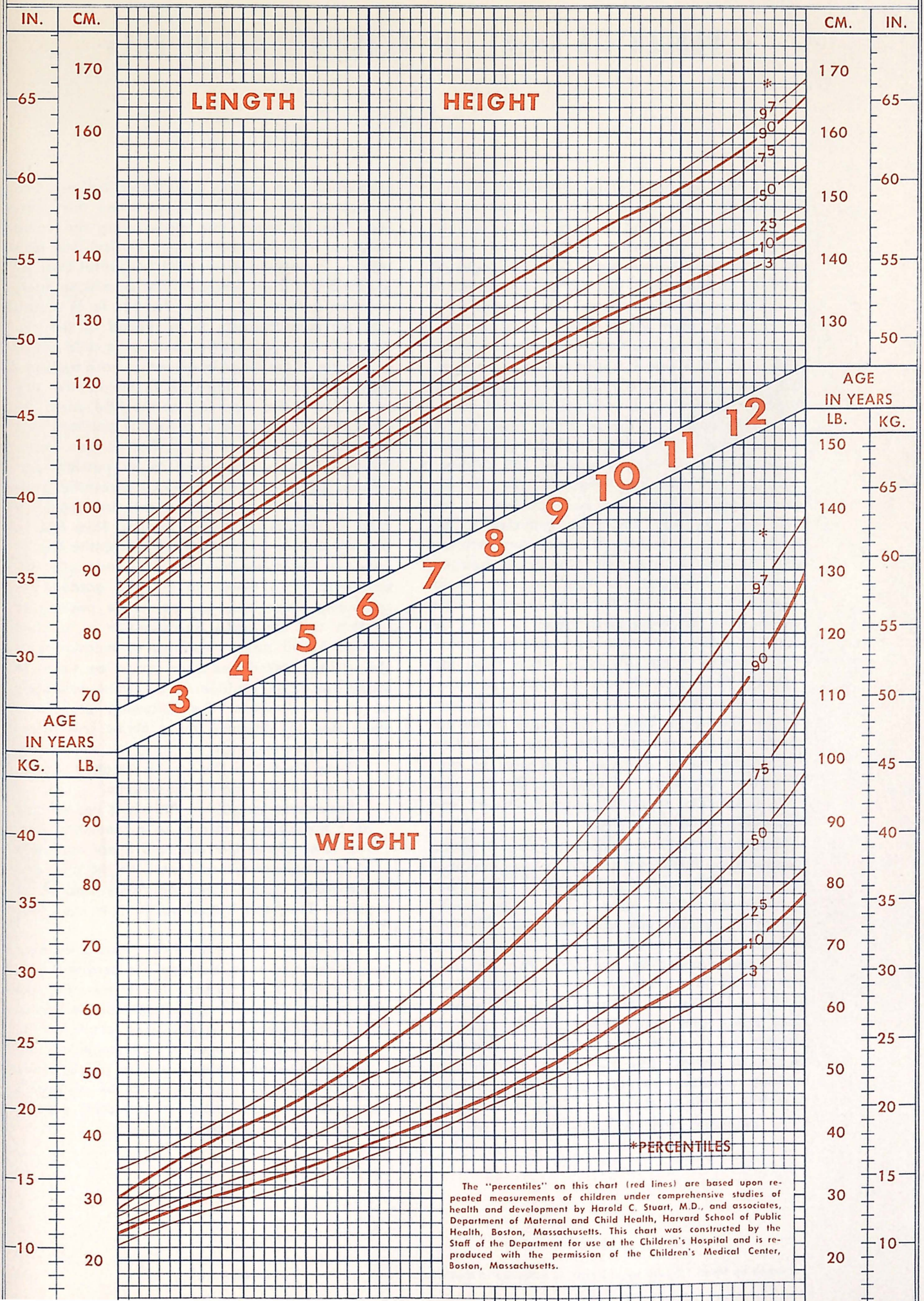
Figure 4

The Children's Medical Center, Boston

Anthropometric Chart.

BOYS

NAME BIRTH DATE NO.



The "percentiles" on this chart (red lines) are based upon repeated measurements of children under comprehensive studies of health and development by Harold C. Stuart, M.D., and associates, Department of Maternal and Child Health, Harvard School of Public Health, Boston, Massachusetts. This chart was constructed by the Staff of the Department for use at the Children's Hospital and is reproduced with the permission of the Children's Medical Center, Boston, Massachusetts.

THE CHILDREN'S MEDICAL CENTER, BOSTON - ANTHROPOMETRIC CHART

PERCENTILE CHART FOR MEASUREMENTS OF BOYS

THIS CHART provides for boys standards of reference for body weight and recumbent length at ages between 2 and 6 years and for weight and standing height from 6 to 13 years. It is based upon repeated measurements at selected ages of a group of more than 100 white boys of North European ancestry living under normal conditions of health and home life in Boston, Mass. The distribution of the measurements obtained from these children at each age is expressed in percentiles, each percentile giving a value which represents a particular position in the normal range of occurrences. The number of the percentile refers to the position which a measurement of the given value would hold in any typical series of 100 children. Thus, the 10th percentile gives the value for the tenth in any hundred; that is, 9 children of the same sex and age would be expected to be smaller in the measurement under consideration while 90 would be expected to be larger than the figure given. Similarly the 90th percentile would indicate that 89 children might be expected to be smaller than the figure given while 10 would be larger. The 50th percentile represents the median or midposition in the customary range. Here, the 10th and 90th percentiles are represented in heavy lines to show the limits within which most children remain. The lighter lines in the graphs divide the distribution into segments for ready recognition and description of individual differences as well as of the "regularity" of progress. The 3rd and 97th percentiles represent unusual though not necessarily abnormal findings.

In line with common usage in the United States, the charts are ruled on a scale in pounds to represent weight. They are ruled, however, in centimeters to represent length under 6 years and height thereafter, because this scale facilitates accuracy in measuring and recording and centimeter rules and tapes are readily available. For the convenience of those preferring them, scales for kilograms and inches are placed outside of the principal scales and paralleling them. Therefore, if weights are taken in kilograms and lengths and heights in inches, they may be plotted directly without conversion by placing a ruler at the appropriate points on the outer scales of the chart.

To determine the percentile position of any measurement at a given age, the vertical age line is located and a dot is placed where this intersects the horizontal line representing the value obtained from the measurement. Vertical lines give age by 2-month intervals and horizontal lines by 2-pound and 2-cm. intervals. This permits by interpolation accurate placement for age to ½ month and for measurements to ½ pound or 0.5 cm. Recognition of the position held by a child within or outside of the range in respect to each measurement recorded calls attention to the relative size and build of the individual at the time. More importantly, comparisons of percentile positions held by these measurements at repeated periodic examinations indicate adherence to or possibly significant deviation from previous percentile positions. Under normal circumstances, one expects a child to maintain a similar position from age to age — that is, on or near one percentile line or between the same two lines. Occasionally encountered sharp deviations or more gradual but continuing shifts from one percentile position to another call for further investigation as to their causes. In all cases, readings of measurements should be checked and care should be taken to secure the same position of the child accurately at all examinations. The following procedures were used in obtaining these norms and therefore are recommended:

Body Weight — The child is weighed without clothing except light undergarments.

Recumbent Length — The child lies relaxed on a firm surface parallel to a centimeter rule. The soles of the feet are held firmly against a fixed upright at the zero mark on the rule, and a movable square is brought firmly against the vertex. The head is held so that the eyes face the ceiling.

Height — The child's heels should be near together, and heels, buttocks and occiput should be against a firm vertical upright mounting the measuring stick. The eyes should be horizontal and approximately in the same plane as the external auditory canals. A right angle triangle or other movable device should be placed firmly on the head at right angles to the measuring stick and the measurement read after a satisfactory position has been adopted.

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Figure 5

Patient J. L., 34.50 months old at examination.

$\frac{BA|AB}{B|B}$ were recorded as tapered.

$\frac{DCBA|ABCD}{DCB|BCD}$ were recorded as hypoplastic.

His birth weight was 5 lbs. 14 oz. He has a patent ductus arteriosus, pulmonary stenosis, and has motor and mental retardation. He had difficulty feeding and became dehydrated 2 months after birth. His mother had rubella at 8 weeks of pregnancy.

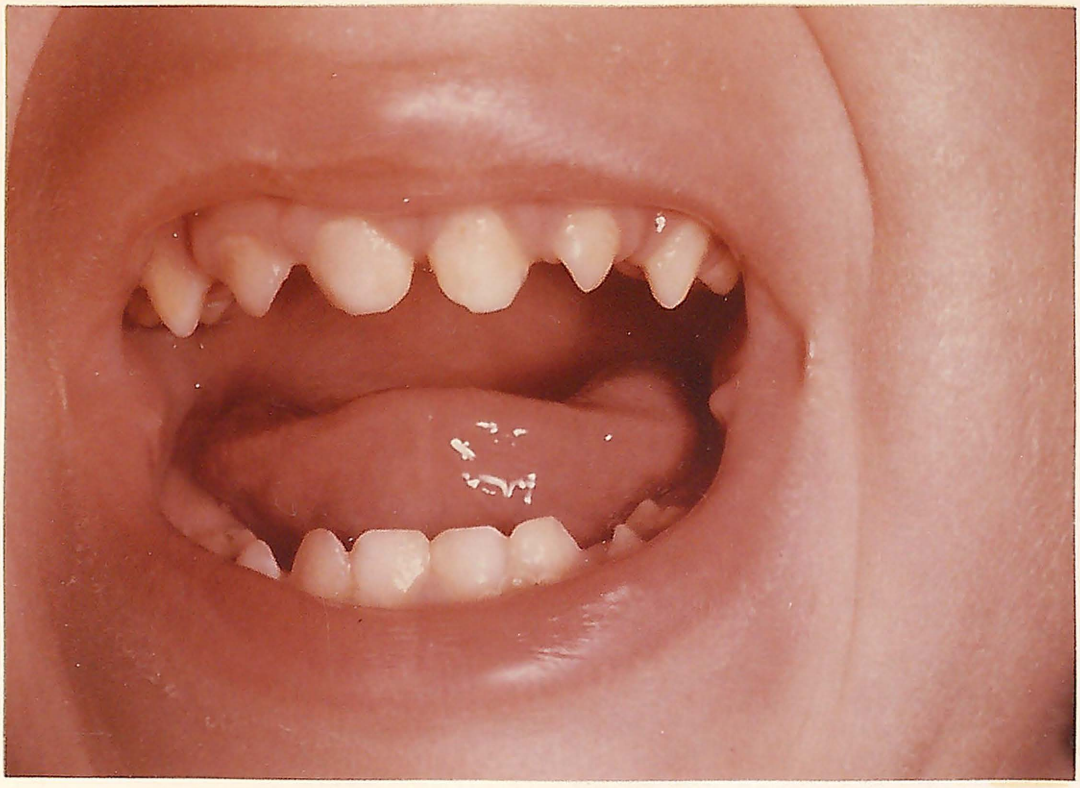

Figure 6

Patient J. M., 34.50 months old at examination.

$\frac{BA}{B} \mid \frac{AB}{B}$ were recorded as tapered.

$\frac{ECBA}{C} \mid \frac{ABCE}{}$ were found to be hypoplastic.

The patient weighed 6 lbs. 11 oz. at birth. She is deaf and has salt and pepper retinopathy of both eyes. Her mother had rubella at 6 weeks of pregnancy although she had received gamma globulin for exposure to rubella 10 days previously.

Figure 7

Patient A. A., 31 months old at examination.

$\frac{A \mid A}{B \mid B}$ were recorded as tapered.

$\frac{B \mid AB}{\quad \mid \quad}$ were recorded as notched.

$\frac{B \mid AB}{D \mid BD}$ were recorded as hypoplastic.

She is deaf. Her mother had rubella at 6 weeks of pregnancy.

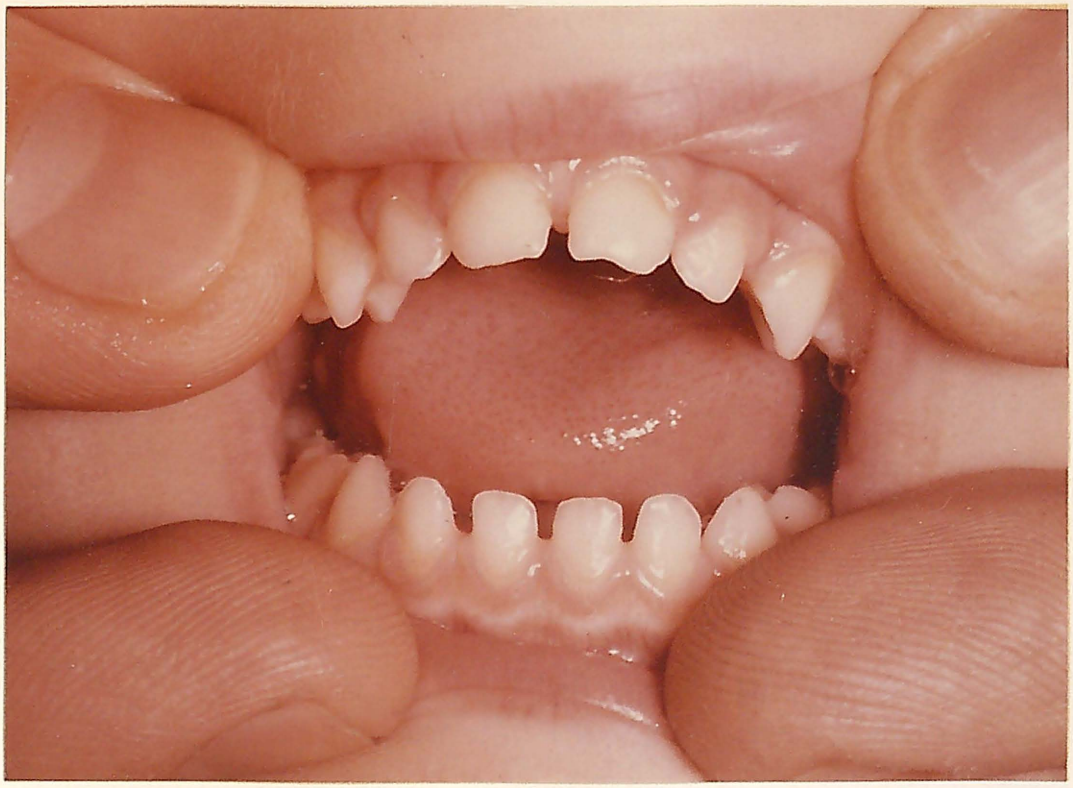

Figure 8

Patient J. O., 29 1/4 months old at examination.

$\frac{BA|AB}{B|AB}$ were recorded as tapered.

$\frac{DBA|ABD}{DB|ABD}$ were recorded as hypoplastic.

He has a patent ductus arteriosus and pulmonary stenosis and is deaf and microcephalic. His birth weight was 5 lbs. 3 oz. and he was 2 weeks premature. His mother had rubella at 10 weeks of pregnancy.

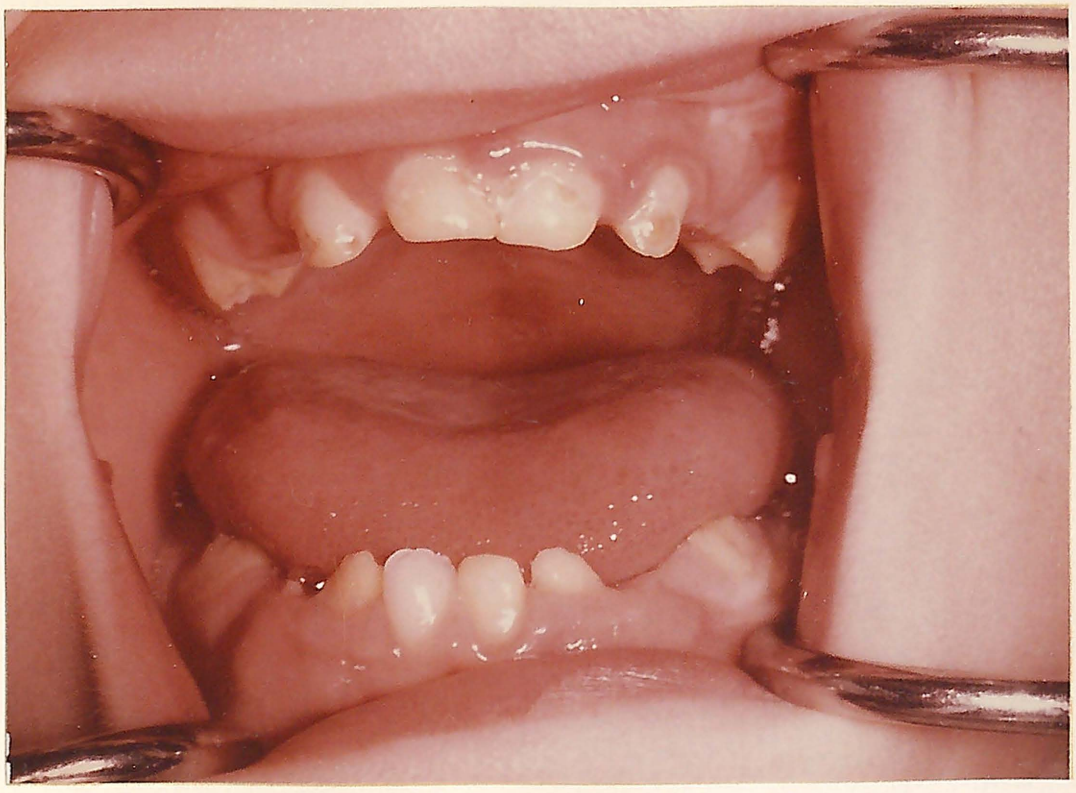

Figure 9

Patient T. B., 30 months old at examination.

$\frac{BA|AB}{B|}$ were recorded as tapered.

All teeth except $\frac{\quad}{A|AB}$ were hypoplastic.

He weighed 4 lbs. 10 oz. at birth, which may have been a month premature. He had congenital thrombocytopenia and splenomegaly and was thought to be microcephalic. His present medical findings include patent ductus arteriosus, pulmonary stenosis, 50 decibel hearing loss, and bilateral chorioretinitis. His mother had rubella at 6 weeks of pregnancy and had received gamma globulin following her exposure.

DISCUSSION

Weller, Alford, and Neva[26] have demonstrated the accuracy of the specific rubella antiboby titer test as an indication of *in utero* infection in children with the manifestations of rubella embryopathy. The determination of such a titer should be a specific feature of a new study of children with rubella embryopathy. Unfortunately, it was not available for inclusion in the present study. Such a test might have excluded any children whose congenital defects were not secondary to rubella embryopathy and whose dental conditions consequently might have masked the findings of a characteristic pattern of dental defects in the true rubella children.

On the basis of the similarity of the symptoms of the study group to those reported by other authors, however, it appears that most of these children were in fact examples of the rubella syndrome. Their birth weights and weights at time of examination were significantly lower ($p < .005$) than those of the children of the control group, and the length of their periods of gestation was normal. This same pattern has been reported by Lundstron[16] and Tartakow[5] and is now recognized as characteristic of children with rubella embryopathy. The high incidence of hearing defects, followed by cardiac anomalies, and less

frequently, eye defects, is the same pattern as reported by Lundstrom,[16] Campbell,[20] and Swan[7] for children with rubella embryopathy. The less common findings of microcephaly, mental and motor retardation, feeding problems, cerebral palsy, and cleft lip and palate have also been reported previously in conjunction with the rubella syndrome. As has been previously reported,[5] a low incidence of neonatal jaundice and thrombocytopenia purpura associated with rubella embryopathy was found in this study.

The sample included in this study might be somewhat different in terms of severity of sequelae than those investigated in earlier studies, inasmuch as a group of 15 children were included whose primary medical diagnosis was hearing loss with few, if any, other medical problems. The very early diagnosis of hearing loss is an infrequent finding in the earlier studies of rubella embryopathy.

The prenatal and neonatal histories of both groups of children were quite similar and were basically non-contributory to the medical and dental findings, with the major exception of the rubella infection of the study group children. Few complaints during pregnancy were reported by the mothers, and most of the mothers had

restricted their intake of drugs and medications to vitamins, calcium, iron, or "water pills." Only 14 mothers reported any difficulty with labor or delivery of the children in either group. It should be noted, however, that no child was eliminated from the control group because of low birth weight or difficulties in the neonatal period or during the mother's pregnancy. Several children in the control group had birth weights of less than 5 1/2 pounds, and others had contracted pneumonia during the first year of life. One child in the control group weighed only three pounds at birth and had received three transfusions to prevent the complications of erythroblastosis fetalis. These findings would partially explain the relatively high incidence of enamel hypoplasia found in the control group. The finding of hypoplasia of the lower cuspids, the most commonly affected tooth in the control group, would appear to be in agreement with the work of Jorgensen[69] who found hypoplastic defects in 16 per cent of the upper and 34 per cent of the lower cuspids of 870 primary cuspids examined.

The experience of obtaining the data by means of direct questioning of the patients' mothers in this study leads to the criticisms previously expressed by others

who have attempted to evaluate the findings of retrospective studies, such as Lundstrom's,[16] which are based upon impersonal questionnaires. This technique cannot probe specifically enough to elicit an adequate response from certain individuals, and the data from these forms are often compiled and interpreted by a variety of individuals, providing the opportunity for subjective variations in classification, diagnosis, analysis, and the life. In the present study the case history of one of the most severely affected rubella children was recorded by the staff of a highly respected institution and yet proved to be insufficiently detailed for an accurate assessment of this child's prenatal history. Thus, the necessity of a consistent direct interviewing technique and examination procedure conducted by the same individual is emphasized.

An attempt was made to relate the variables of medical diagnosis, birth weight, gestation period, time of exposure to rubella, and other factors, either singly or in combinations. No pattern was apparent, although it is possible that a more extensive statistical analysis of the data could shed additional light on the pattern of variables which characterizes this group of rubella

children. Time did not permit the completion of a stepwise multiple regression of the data but the use of this further analysis of the data is planned as a part of the continuing study of this group of rubella children.

Additional features of the continuation of this study should include the determination of rubella antibody titers, cephalometric analysis, and the collection of study model casts and intra-oral radiographs.

It is possible that the five children in the study group who did not have enamel hypoplasia were not examples of rubella embryopathy. Three of these children were congenitally deaf only, and the other two presented cardiac anomalies which are not characteristic of the rubella syndrome. It was apparent from this study, however, that less severe forms of enamel hypoplasia are associated with the less severe physical manifestations of the rubella syndrome.

A comparison of the birth weights of the study group children with the percentage incidence of hypoplasia revealed the following relationships, which are not statistically significant for this group of children but are of interest in light of Stein's work with hypoplasia of prematurity:

Birth Weight	Number of Children	Percentage of Teeth With Enamel Hypoplasia
6 pounds or more	24	30
5 1/2 to 6 pounds	11	33
Less than 5 1/2 pounds	15	45

The children in the study group whose birth weight was low may have a higher incidence of enamel hypoplasia. However, about one-half of the children in the study group who had enamel hypoplasia similar to Stein's[38] hypoplasia of prematurity weighed more than 5 1/2 pounds at birth. For the further study of this variable, the hypoplastic defects should be classified and scored according to a more detailed scheme, perhaps based upon the system proposed by Darling for his study of amelogenesis imperfecta. A collection of exfoliated teeth for sectioning and histologic study might aid in the classification of the enamel defects, although it is anticipated that most of the hypoplasia in the posterior teeth will be subject to abrasion and thereby limit the microscopic analysis of the defects.

In view of the findings of this study, it is doubtful that all of the children examined by Lundstrom[56] and Grahnén[57] had been infected with *in utero* rubella since they had no medical abnormalities other than those seen in one of Grahnén's patients who presented with both medical and dental defects. The results of the present

study do not support their conclusion that enamel hypoplasia does not occur in conjunction with rubella embryopathy.

Lundstrom[56] reported delayed eruption in children (13-18 months of age) as did Evans in a similar study. Again, the present study did not find significantly fewer erupted teeth in the study group children. The study group patients who were outside Lysell's minus second standard deviation for eruption of the primary teeth (which was used to determine the progress of eruption) also represented the most severely medically handicapped children of the study group. It follows that any clinically apparent delayed eruption might be attributed directly to the effects of the rubella syndrome or represent a secondary effect of the embryopathy and a direct result of the general medical disability of the child.

The results of this study suggest that the assessment of tooth eruption should be made before the child's complete deciduous dentition would be normally erupted, i.e., the child should be examined between 12 and 24 months of age.

The findings of Evans[53] related to hypoplasia can not be readily compared to those of this study since no

description of the criteria for classification of enamel hypoplasia was included, nor were there illustrative sketches or photographs for reference.

Evans[53] mentioned but did not describe the occurrence of a restricted arch form, which might have been similar to that seen in Figure 8, which illustrates the lingual version of the lower anterior teeth. Such an arch can not be described as "restricted" without an analysis of cephalometric radiographs and study casts, however.

The statistically significant finding that children with rubella embryopathy had notched incisal edges and a tapering of the incisal third of their anterior teeth is interesting in the light of work by Kraus,[58] who has shown that the shape of the teeth is largely determined by mitotic activity of the cell layer of the inner enamel epithelium. Since Plotkin[33] has shown the rubella virus to be capable of reducing mitotic activity, it is conceivable that the tapered teeth result from the action of the virus upon the inner enamel epithelium of the developing tooth. In this regard, Kraus indicates that the tooth arises from one center and subsequently develops its distinctive shape by elevation of the mesial and distal portions adjacent to the original conical center.

The notching of the incisal edge has been described in permanent teeth in conjunction with syphilis, a relationship not clearly understood. Alford[27] has mentioned a similarity of the reactions of the fetus affected by rubella to that of one infected with syphilis. Perhaps a histologic study, infecting monkeys with rubella and with syphilis under controlled conditions, could be designed to study the effect of the rubella virus on the dentition at various stages of development.

SUMMARY

Fifty children (average age 2 1/2 years) with congenital abnormalities attributed to *in utero* infection with rubella were examined for dental defects. The results of this examination were compared with the results of the dental examination of 50 normal 2 to 3 year old children examined at a welfare medical clinic. A medical history was obtained from the parents of the children in each group. The prenatal and neonatal histories were very similar for each group and were generally non-contributory, except for the incidence of rubella in the study group. Although a greater incidence of post-natal illnesses and/or surgical procedures was found in the study group, these were believed to have occurred too late during tooth development to have affected the primary teeth.

The children in the study group had a statistically significantly lower birth weight but a normal length of gestation. The children also weighed less at the time of examination than did the control group.

No gross abnormalities were found in the soft tissues, tongue, cheeks, or mandibular-maxillary relationships of the patients in either group. One child in the study group had a cleft of the lip and palate; and one child in

the study group and one child in the control group had dental caries.

Enamel hypoplasia (defined as defects of enamel detected with an explorer) was found in 45 (90 per cent) of the study group and 13 (26 per cent) of the control group.

Tapered teeth (defined as an abnormal constriction of the mesial and/or distal portion of any anterior tooth) occurred in 78 per cent of the children in the study group and 18 per cent of the control group.

Nine children (18 per cent) of the study group had notched teeth, which were not found in the control group.

The higher incidence of enamel hypoplasia, tapered teeth, and notched teeth in the study group was found to be statistically significant ($p<.005$).

Even though several children in the study group appeared clinically to have delayed eruption, the difference from the control group was not statistically significant. The data was considered inadequate to confirm the incidence of delayed eruption in conjunction with rubella embryopathy.

CONCLUSIONS

1. Enamel hypoplasia of the primary teeth is a sequela of intrauterine infection with rubella and occurred in 90 per cent of the children with rubella embryopathy in this study.

2. Enamel hypoplasia was more common in females in both the rubella and control groups.

3. Tapering of the incisal one third of the primary anterior teeth is an indication of rubella embryopathy and occurred in 78 per cent of the children with rubella embryopathy studied.

4. Notching of the incisal edge of the primary anterior teeth is a sequela of intrauterine infection with rubella and occurred in 18 per cent of the children with rubella embryopathy studied.

5. The average incidence of hypoplastic, tapered, and notched teeth was higher in the children with rubella embryopathy than in the children in the control group.

6. No association was found between the dental defects and the other physical defects found in children with rubella embryopathy in this study.

7. Low birth weight with normal length of gestation was a more common finding in the children with rubella embryopathy studied.

8. Children with rubella embryopathy weighed less on the average at 2 1/2 years of age than the children in the control group when weighed at a comparable age.

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CURRICULUM VITAE

Robert Jay Musselman

Date and Place of Birth

April 24, 1939, Warsaw, Indiana

Education

North Side High School, Fort Wayne, Indiana, 1954-57

Indiana University, Bloomington, Indiana, 1957-60

Indiana University School of Dentistry

Indianapolis, Indiana, 1960-64 (D.D.S.,1964)

James Whitcomb Riley Hospital for Children

Indianapolis, Indiana

Pedodontic Intern 1964-65

Pedodontic Resident 1965-66

Indiana University School of Dentistry

Graduate School, 1966-68

Professional Societies

American Dental Association

Indiana State Dental Society

Indianapolis District Dental Society

American Society of Dentistry for Children

American Association of Dental Schools

American Society of Hospital Dentists

ABSTRACT

DENTAL DEFECTS AND RUBELLA EMBRYOPATHY: A CLINICAL STUDY OF FIFTY CHILDREN

Robert Jay Musselman
1121 West Michigan Street
Indianapolis, Indiana
46202

This study reports the results of the clinical examination of fifty 2 1/2 year old children with congenital defects attributed to infection with prenatal rubella. The results were compared with the results of the clinical examination of fifty normal 2 to 3 year old children

The children with congenital defects attributed to *in utero* rubella infection had a significantly lower ($p<.005$) weight at birth and at 2 1/2 years of age. These findings, along with the type and distribution of congenital defects, are in agreement with other reports of children with confirmed rubella embryopathy.

The fifty children with rubella embryopathy had a significantly ($p<.005$) higher incidence of dental defects. Of the rubella children studied, 90 per cent had enamel hypoplasia, 78 per cent had tapered teeth, and 18 per cent had notched anterior teeth. Among the normal children studied, 26 per cent had enamel hypoplasia, 18 per cent had tapered teeth, and none had notched teeth. No other dentofacial abnormalities other than a cleft of the lip and palate in one rubella child were found.